ORIGINAL ARTICLE

A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong

Nelson Lee, M.D., David Hui, M.D., Alan Wu, M.D., Paul Chan, M.D., Peter Cameron, M.D., Gavin M. Joynt, M.D., Anil Ahuja, M.D., Man Yee Yung, B.Sc., C.B. Leung, M.D., K.F. To, M.D., S.F. Lui, M.D., C.C. Szeto, M.D., Sydney Chung, M.D., and Joseph J.Y. Sung, M.D.

ABSTRACT

BACKGROUND

There has been an outbreak of the severe acute respiratory syndrome (SARS) worldwide. We report the clinical, laboratory, and radiologic features of 138 cases of suspected SARS during a hospital outbreak in Hong Kong.

METHODS

From March 11 to 25, 2003, all patients with suspected SARS after exposure to an index patient or ward were admitted to the isolation wards of the Prince of Wales Hospital. Their demographic, clinical, laboratory, and radiologic characteristics were analyzed. Clinical end points included the need for intensive care and death. Univariate and multivariate analyses were performed.

RESULTS

There were 66 male patients and 72 female patients in this cohort, 69 of whom were health care workers. The most common symptoms included fever (in 100 percent of the patients); chills, rigors, or both (73.2 percent); and myalgia (60.9 percent). Cough and headache were also reported in more than 50 percent of the patients. Other common findings were lymphopenia (in 69.6 percent), thrombocytopenia (44.8 percent), and elevated lactate dehydrogenase and creatine kinase levels (71.0 percent and 32.1 percent, respectively). Peripheral air-space consolidation was commonly observed on thoracic computed tomographic scanning. A total of 32 patients (23.2 percent) were admitted to the intensive care unit; 5 patients died, all of whom had coexisting conditions. In a multivariate analysis, the independent predictors of an adverse outcome were advanced age (odds ratio per decade of life, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio per 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04).

CONCLUSIONS

SARS is a serious respiratory illness that led to significant morbidity and mortality in our cohort.

From the Departments of Medicine and Therapeutics (N.L., D.H., A.W., C.B.L., S.F.L., C.C.S., J.J.Y.S.), Microbiology (P. Chan), Emergency Medicine (P. Cameron), Anesthesia and Intensive Care (G.M.J.), Diagnostic Radiology and Organ Imaging (A.A.), Surgery (M.Y.Y., S.C.), and Anatomical and Cellular Pathology (K.F.T.), Chinese University of Hong Kong, Hong Kong, China. Address reprint requests to Dr. Sung at the Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China, or at joesung@cuhk.edu.hk.

This article was published at www.nejm.org on April 7, 2003.

In March 2003, there was an outbreak of atypical pneumonia in Hong Kong. As of March 27, there were 367 reported cases in Hong Kong and more than 1400 cases worldwide.[1] The disease may progress rapidly and often results in the acute respiratory distress syndrome (ARDS). As of this writing, there have been 10 deaths in Hong Kong related to the illness, which the World Health Organization (WHO) has named the severe acute respiratory syndrome (SARS). Globally, there have been at least 53 deaths related to SARS.[1] Schools have been closed in Hong Kong, and more than 1000 people who had a history of contact with a patient with SARS were quarantined.

We describe the clinical, laboratory, and radiologic features of patients with SARS who were seen at the Prince of Wales Hospital, Hong Kong. These patients were either health care workers in a medical ward of the hospital or persons who had a history of contact with an index patient or exposure to the same medical ward. We also included patients who had contracted the disease through direct contact with these cases.

METHODS

On March 10, 18 health care workers in a medical ward of the Prince of Wales Hospital reported that they were ill. Through telephone contact, more than 50 of the hospital's health care workers were identified as having had a febrile illness over the previous few days. On March 11, 23 of them were admitted to an isolation ward in the hospital. A team of "atypical pneumonia physicians" was formed to take responsibility for screening of suspected cases and subsequent management. The team included physicians from the Department of Medicine and Therapeutics (infectious disease, respiratory medicine, and general medicine), the Department of Emergency Medicine, and the intensive care unit (ICU). Clinical findings and laboratory data were documented prospectively.

Since the etiologic agent was not known at the onset of the outbreak, the diagnosis was based on clinical symptoms and the ruling out of common bacterial and viral pathogens that cause pneumonia. On the basis of the criteria for SARS that have been established by the Centers for Disease Control and Prevention (CDC),[2] our case definition was a fever (temperature, >38°C), a chest radiograph (a plain radiograph, a computed tomographic [CT] image of the thorax, or both) showing evidence of consolidation with or without respiratory symptoms (e.g., cough and shortness of breath), and a history of exposure to an index patient suspected to have SARS or direct contact with a person who became ill after exposure to an index patient.

All patients were initially admitted to medical wards with isolation facilities. Initial investigations included a complete blood count (with a differential count), clotting profile (prothrombin time, activated partial-thromboplastin time, international normalized ratio, D-dimer) and serum biochemical measurements (including electrolytes, renal-function and liver-function values, creatine kinase, and lactate dehydrogenase). These studies and chest radiography were performed daily until the fever had subsided for three days. Nasopharyngeal-aspirate samples obtained from all study patients were screened for common viruses, including influenzavirus A and B, respiratory syncytial virus, adenovirus, and parainfluenzavirus types 1, 2, and 3, with the use of commercial immunofluorescence assays. In addition, virus culture was performed with the use of various cell lines (LLC-MK2, MDCK, Hep2, human embryonic lung fibroblast, Buffalo green-monkey kidney, and Vero cells). In addition, multiplex reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays for influenzavirus A, influenzavirus B, and respiratory syncytial virus were performed in 65 randomly selected patients. Electron microscopy was used to study nasopharyngeal aspirates in selected cases. Sputum cultures and blood cultures were performed in all cases to complete the microbiologic workup. PCR assays for mycoplasma and *Chlamydia pneumoniae* were performed in 65 randomly selected patients. A legionella urinary antigen assay was performed in the first 25 patients.

Initial treatment included cefotaxime and clarithromycin (or levofloxacin) to target common pathogens causing community-acquired pneumonia, according to current recommendations.[3,4] Oseltamivir (Tamiflu) was also given initially to treat possible influenza infection. If fever persisted for more than 48 hours and the blood count showed leukopenia, thrombocytopenia, or both, oral ribavirin (1.2 g three times a day) and corticosteroid therapy (prednisolone at a dose of 1 mg per kilogram of body weight per day) was given as a combined regimen. Patients with persistent fever and worsening lung opacities were given intravenous ribavirin (400 mg every eight hours) and corticosteroid therapy (an additional two to three pulses of 0.5 g of methylprednisolone daily). Patients in whom hypoxemia developed were given oxygen through a nasal can-

nula. Patients were admitted to the ICU if respiratory failure developed, as evidenced by an arterial oxygen saturation of less than 90 percent while the patient was receiving 50 percent supplemental oxygen, a respiratory rate that exceeded 35 breaths per minute, or both.

An epidemiologic study was conducted shortly after the outbreak. We identified our index patient, whose exposure history has been described elsewhere.[5] He was a 26-year-old ethnic Chinese man who was admitted to the Prince of Wales Hospital on March 4, 2003, with a high temperature, myalgia, and cough. His chest radiograph showed an ill-defined air-space opacity in the periphery of the right upper lobe. He was treated with amoxicillin–clavulanate and clarithromycin. All bacteriologic and virologic tests were unrevealing. The right lung opacity progressed to bilateral consolidation. After seven days of antibiotic therapy, his fever gradually diminished, and the lung opacities started to resolve. During this period, he was treated with albuterol (0.5 mg through a jet nebulizer, delivered by oxygen at a flow rate of 6 liters per minute, four times daily for a total of seven days).

From our contact tracing, we found that the first patients began to have symptoms two days after the index patient's admission. Moreover, all doctors and nurses who participated in the care of the patient, all medical students who had examined him, and the patients around him were the ones who first reported febrile illness, on March 10. We therefore defined all cases that developed in persons who had had direct contact with the index patient or who had been exposed to him in the medical ward as secondary cases. Cases in patients who contracted the disease from these patients (e.g., family members of health care workers or of patients who had stayed in this medical ward) were defined as tertiary cases.

STUDY POPULATION AND DATA ANALYSIS

Our study cohort included all secondary and tertiary cases. Their demographic, clinical, laboratory, and radiologic characteristics were reported and analyzed. The clinical composite end point was the need for care in the ICU, death, or both. Univariate and multivariate analyses of clinical and laboratory data were performed to identify prognostic variables. Statistical analysis was performed with SYSTAT software (version 7.0, SPSS, Chicago). Data are reported as means ±SD unless otherwise specified. Univariate analysis was performed to compare patients who reached the end point and those who did not, with the use of an unpaired Student's t-test or chi-square test, as appropriate. Multivariate logistic-regression analysis was then performed, with backward stepwise analysis, to identify independent predictors of the end point. All comparisons of clinical variables with a P value of less than 0.20 by univariate analysis were entered into the model. A P value of less than 0.05 was considered to indicate statistical significance. All probabilities are two-tailed.

RESULTS

Between March 11 and March 25, 2003, a total of 156 patients were hospitalized with SARS, of whom 138 were identified as having either secondary or tertiary cases as a result of exposure to our index patient. There were 112 patients with secondary cases and 26 with tertiary cases in this cohort, including 69 health care workers (20 doctors, 34 nurses, and 15 allied health workers) and 16 medical students who had worked in the index ward, plus 53 patients who were either in the same medical ward or had visited their relatives there. There were 66 male patients and 72 female patients; their mean age was 39.3±16.8 years. A total of 19 patients had coexisting conditions: cardiovascular disease in 4, the myelodysplastic syndrome in 2, chronic liver disease in 3, diabetes mellitus in 5, chronic renal failure in 2, and chronic pulmonary disease in 3. Most of the health care workers were previously healthy. All patients were ethnic Chinese.

CLINICAL FEATURES

The interval between exposure to the index patient or ward and the onset of fever ranged from 2 to 16 days. The median incubation period was six days. The most common symptoms at presentation were fever (in 100 percent of the patients); chills, rigor, or both (73.2 percent); myalgia (60.9 percent); cough (57.3 percent); headache (55.8 percent); and dizziness (42.8 percent). Less common symptoms included sputum production (in 29.0 percent), sore throat (23.2 percent), coryza (22.5 percent), nausea and vomiting (19.6 percent), and diarrhea (19.6 percent). Physical examination on admission revealed a high body temperature in most patients (median temperature, 38.4°C; range, 35 to 40.3°C). Inspiratory crackles could be heard at the base of the lung. Wheezing was absent except in one patient with a history of asthma. Rash, lymphadenopathy, and purpura were not seen in this cohort.

HEMATOLOGIC FINDINGS

The initial blood count showed leukopenia (total white-cell count, <3.5×10⁹ per liter) in 33.9 percent of patients. Whereas the neutrophil count (median, 3500 per cubic millimeter; range, 500 to 11,800) and the monocyte count were normal in most cases, 69.6 percent of the patients had moderate lymphopenia (absolute lymphocyte count, <1000 per cubic millimeter). Thrombocytopenia (platelet count, <150,000 per cubic millimeter) was documented in 44.8 percent of the patients on presentation. The lymphocyte count continued to drop within the first few days after admission (Table 1). A prolonged activated partial-thromboplastin time (>38 seconds) was noted in 42.8 percent of the patients, whereas the prothrombin time remained normal in most cases. In 45.0 percent of the patients, the D-dimer level was also elevated. Reactive lymphocytes were detected in peripheral-blood films in 15.2 percent of cases.

BIOCHEMICAL FINDINGS

Serum chemical values were normal in the majority of cases. There were, however, several abnormalities in a substantial proportion of patients. Serum alanine aminotransferase levels were elevated (>45 IU per milliliter) in 23.4 percent of patients (mean level, 60.4±150.4 IU per milliliter); only two patients had a history of chronic liver disease. Creatine kinase levels were elevated in 32.1 percent of patients (median level, 126 U per liter; range, 29 to 4644). None of the patients with elevated creatine kinase levels had abnormal values for creatine kinase MB or troponin T, indicating that the source of creatine kinase was unlikely to be cardiac muscles. The lactate dehydrogenase level was elevated in 71.0 percent of patients. Hyponatremia (sodium level, <134 mmol per liter) was documented in 20.3 percent of patients, and hypokalemia (potassium level, <3.5 mmol per liter) in 25.2 percent of patients. The results of laboratory tests performed during the first week of hospitalization are listed in Table 1.

MICROBIOLOGIC AND VIROLOGIC FINDINGS

In our cohort of 138 patients, there were five positive sputum cultures; three were positive for *Haemophilus influenzae*, one for *Streptococcus pneumoniae*, and one for *Klebsiella pneumoniae*. None of the blood cultures were positive. Other bacteriologic investigations were unrevealing. Of all the nasopharyngeal aspirates collected, one was positive for influenzavirus A, one was positive for influenzavirus B,

Table 1. Mean (± SD) Laboratory Results in 138 Patients in Our Study Cohort during the First Seven Days of Hospitalization.

Variable*	Day 1	Day 3	Day 5	Day 7
Hemoglobin (g/dl)	13.5±1.7	13.1±1.7	13.0±1.6	12.9±1.7
Platelets (×10⁻⁹/liter)	150.2±60.1	153.2±61.3	164.9±70.7	206.3±89.9
White cells (×10⁻⁹/liter)	5.1±2.1	5.1±2.7	6.0±3.4	8.3±4.9
Neutrophils (×10⁻⁹/liter)	3.9±2.0	4.0±2.7	5.0±3.3	7.2±4.7
Lymphocytes (×10⁻⁹/liter)	0.9±0.7	0.8±0.7	0.7±0.4	0.6±0.4
Prothrombin time (sec)	11.2±4.7	12.7±8.6	11.2±4.6	11.3±4.0
Activated partial-thromboplastin time (sec)	41.6±8.9	44.8±12.8	41.2±8.1	36.3±6.9
Sodium (mmol/liter)	135.6±3.4	135.9±3.5	137.0±4.4	139.2±4.9
Potassium (mmol/liter)	3.7±0.4	3.8±0.5	3.8±0.4	3.9±0.4
Urea (mmol/liter)	4.7±5.1	4.5±4.5	4.6±3.8	6.3±7.2
Creatinine (μmol/liter)	99.0±111.8	94.3±100.4	82.8±23.8	82.7±27.2
Bilirubin (mmol/liter)	10.0±19.4	10.7±17.8	12.5±19.3	14.3±16.3
Alanine aminotransferase (IU/liter)	60.4±150.4	67.4±113.7	69.4±72.3	89.8±104.5

* To convert values for creatinine to milligrams per deciliter, divide by 88.4, and to convert values for bilirubin to milligrams per deciliter, divide by 17.1.

and two were positive for respiratory syncytial virus. Microscopical examination of nasopharyngeal aspirates from five patients showed paramyxovirus-like viral particles in one and coronavirus-like viral particles in another. The aspirates from the other three patients were negative. Further virologic studies are in progress.

FINDINGS ON CHEST RADIOGRAPHS

At the onset of fever, 108 of the 138 patients (78.3 percent) had abnormal chest radiographs, all of which showed air-space consolidation. Of these 108 patients, 59 (54.6 percent) had unilateral focal involvement (Fig. 1) and 49 (45.4 percent) had either unilateral multifocal or bilateral involvement. Air-space opacities developed in all patients eventually during the course of the disease.

The initial radiographic changes were indistinguishable from those associated with other causes of bronchopneumonia. Interestingly, peripheral-zone involvement was predominant. Pleural effusion, cavitation, and hilar lymphadenopathy were absent in our cohort. Among patients with clinical deterioration, serial chest radiographs showed progression of pulmonary infiltrates approximately 7 to 10 days after admission. Lung opacities enlarged, and multiple areas of involvement were often seen (Fig. 2A and 2B). A successful response to therapy could be demonstrated by serial chest radiographs showing the resolution of lung opacities (Fig. 2C). In cases in which typical lung opacities could not be found on the initial plain chest radiograph, conventional and high-resolution CT images of the thorax proved to be useful. The typical finding on thoracic CT images, as shown in 25 cases, was ill-defined, ground-glass opacification in the periphery of the affected lung parenchyma, usually in a subpleural location (Fig. 3). The characteristic peripheral alveolar opacities were very similar to those found in bronchiolitis obliterans organizing pneumonia.[6,7] There was no obvious bronchial dilatation.

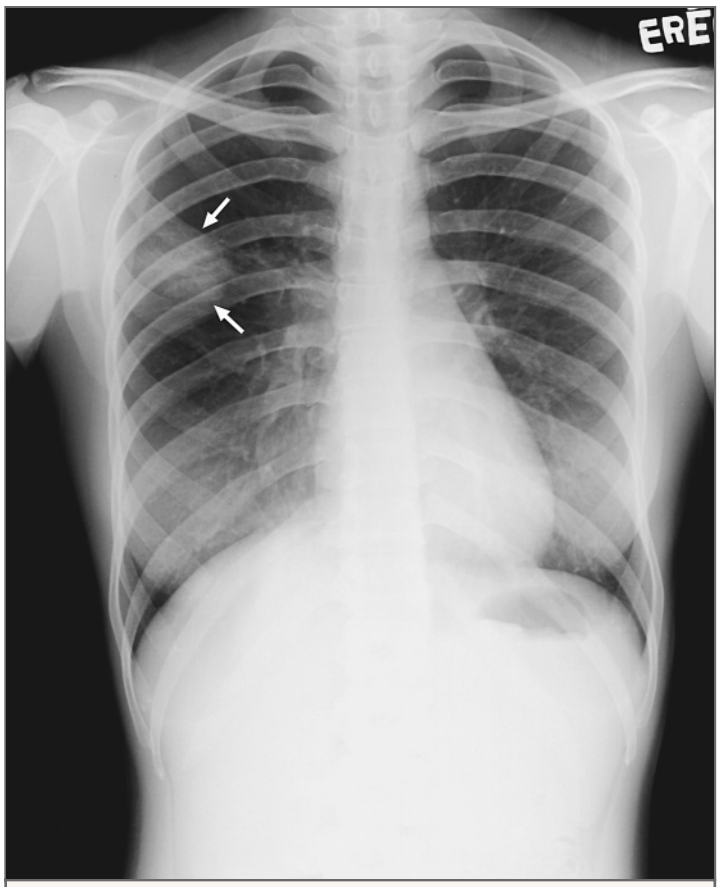


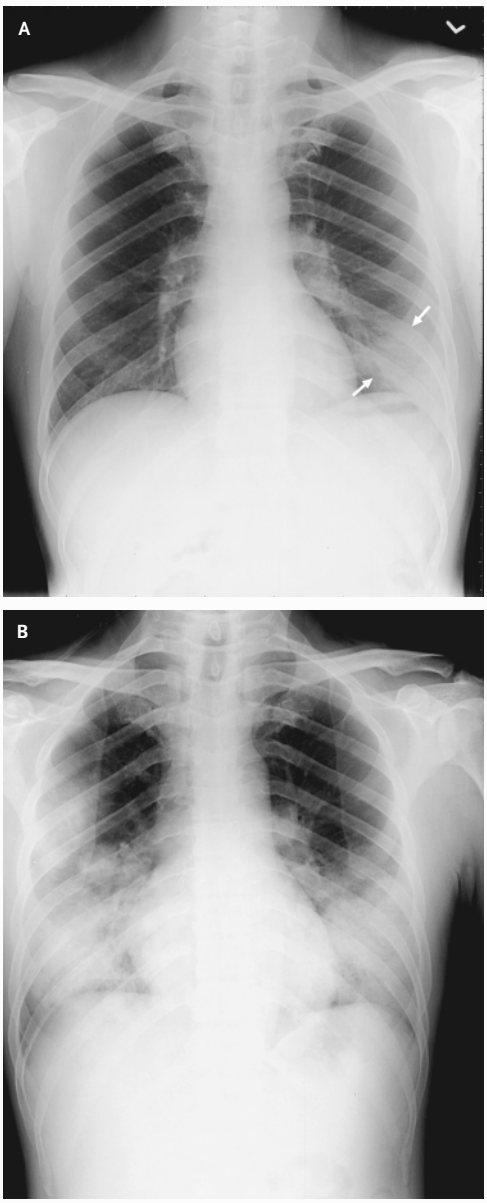
Figure 1. Frontal Chest Radiograph in a 25-Year-Old Woman Showing Ill-Defined Air-Space Shadowing (Arrows).
There is no associated pleural effusion or hilar or mediastinal adenopathy.

CLINICAL OUTCOMES

Of the 138 patients, 32 (23.2 percent) were admitted to the ICU, all because of respiratory failure. Mechanical ventilatory support with positive end-expiratory pressure was required in 19 patients (13.8 percent). Among the 32 patients in the ICU, dramatic increases in lung opacity, shortness of breath, and hypoxemia occurred at a median of 6.5 days (range, 3 to 12) and led to their ICU admission. By day 21 of the outbreak, five patients had died (crude mortality rate, 3.6 percent). All five had originally been admitted because of major medical conditions. Two patients had the myelodysplastic syndrome, one had congestive heart failure, one had alcoholic liver cirrhosis, and one had a reactivation of hepatitis B. None of the health care workers or medical students died. To date, a total of 76 patients (55.1 percent) have been discharged, of whom 44 (31.9 percent) were health care workers. Fitness for discharge was based on defervescence for at least 96 hours, with radiographic evidence of improvement in lung consolidation.

FACTORS PREDICTIVE OF ICU ADMISSION AND DEATH

Univariate analysis showed that advanced age, male sex, a high peak creatine kinase value, a high lactate



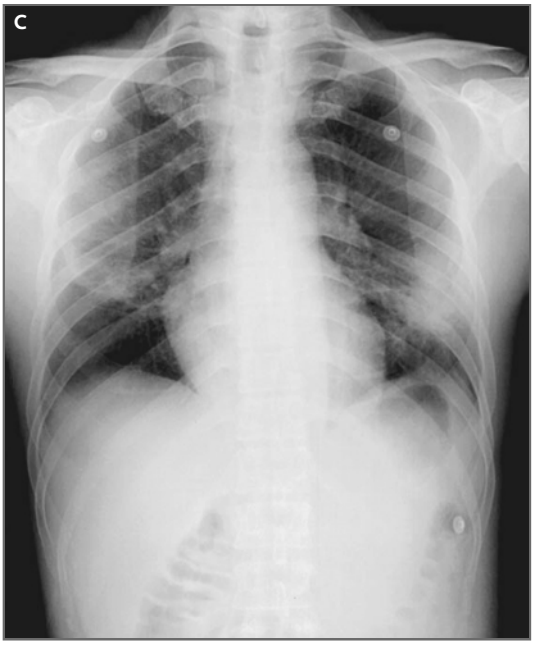


Figure 2. Frontal Chest Radiographs in a 46-Year-Old Man.
Panel A shows an obvious area of air-space shadowing (arrows) on the left side. A follow-up chest radiograph showed progression of the disease, with multiple, bilateral areas of involvement (Panel B). A subsequent chest radiograph shows improvement of bilateral lung opacities after therapy (Panel C).

dehydrogenase level on presentation and a high peak value, a high initial absolute neutrophil count, and a low serum sodium level were significant predictive factors for ICU admission and death (Table 2). The presence of coexisting conditions (in 19 patients) did not appear to be associated with a worse clinical outcome (P=0.14). On multivariate analysis, the only factors that were predictive of an adverse outcome were advanced age (odds ratio for every 10 years of age, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio for every 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04).

POSTMORTEM FINDINGS

Postmortem examination in two cases showed gross consolidation of the lungs. Histologic features varied from region to region. The early phase and organizing phase of diffuse alveolar damage were seen in different parts of the lung. The early phase was characterized by pulmonary edema with hyaline membrane formation suggestive of the early phase of ARDS (Fig. 4). Cellular fibromyxoid organizing exudates in air spaces indicated the organizing phase of alveolar damage. There was a scanty lymphocytic inflammatory infiltrate in the interstitium.

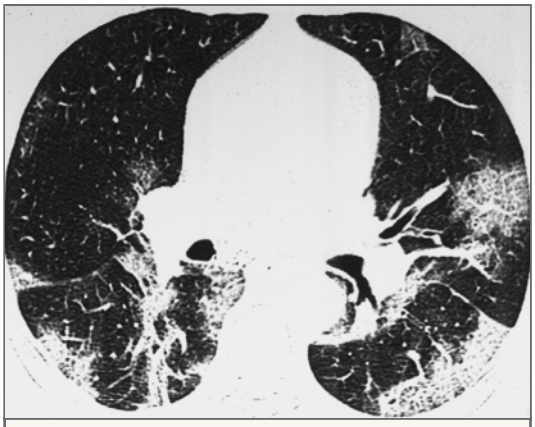


Figure 3. A High-Resolution CT Scan Showing the Characteristic Ground-Glass Abnormality in a Subpleural Location.

There is no cavitation. A conventional CT scan did not show pleural effusion or lymphadenopathy.

Vacuolated and multinucleated pneumocytes were also identified. Viral inclusions were not detected. There was no evidence of the involvement of other organs.

DISCUSSION

We report an outbreak in our hospital of a deadly pneumonia, which caused rapid deterioration of pulmonary function requiring ICU admission in 23.2 percent of cases and mechanical ventilation in 13.8 percent. Within a period of less than two months, SARS has become a global health problem, prompting the WHO to issue a global alert for the first time in more than a decade.[1]

SARS developed in 69 health care workers and 16 medical students, all with unremarkable medical histories, after exposure at work in the medical ward for men where our index patient was hospitalized. The high infectivity was also demonstrated by the fact that there were 26 tertiary cases, which included family members of the infected health care workers. We suspected that the infection was transmitted by droplets and possibly by fomites, and we therefore instituted both airborne precautions (e.g., use of the N-95 respirator) and contact precautions (e.g., use of gowns and gloves), as recommended by the CDC.[8] However, the use of a jet nebulizer to administer aerosolized albuterol in the index patient had probably aggravated the spread of the disease by droplet infections.

Table 2. Univariate Analyses of Clinical and Laboratory Variables Associated with the Combined Outcome of ICU Care or Death.*

Variable	No ICU Care	ICU Care or Death	P Value
Age (yr)	36.1±14.6	50.2±18.4	0.007
Male sex (%)	41.9	66.7	0.01
Peak D-dimer (ng/ml)	951.0±1197.9	1686.9±2132.3	0.31
Platelets ($\times 10^{-9}$/liter)	156.8±61.2	131.7±64.9	0.06
Neutrophils ($\times 10^{-9}$/liter)	3.7±1.9	4.6±2.1	0.02
Lymphocytes ($\times 10^{-9}$/liter)	0.9±0.7	0.8±0.5	0.49
Activated partial-thromboplastin time (sec)	41.0±7.5	43.6±11.7	0.23
Sodium (mmol/liter)	136.1±2.7	134.0±4.6	0.02
Urea (mmol/liter)	3.8±1.1	7.3±9.6	0.05
Creatinine (μmol/liter)†	86.1±19.4	135.5±218.0	0.21
Alanine aminotransferase (IU/liter)	46.5±81.4	99.4±262.0	0.27
Creatine kinase (U/liter)			
On presentation	268.5±434.8	609.3±973.2	0.06
Peak	352.7±544.0	697.4±971.1	0.04
Lactate dehydrogenase (U/liter)			
On presentation	287.7±143.3	558.0±258.0	<0.001
Peak	310.0±153.8	629.7±283.5	<0.001

* Plus–minus values are means ±SD.
† To convert values for creatinine to milligrams per deciliter, divide by 88.4.

The clinical presentation and radiologic features of SARS bear some resemblance to the syndrome commonly referred to as "atypical pneumonia"; mycoplasma, chlamydia, and legionella are the usual pathogens implicated in this syndrome. Fever, chills, headache, myalgia, and dry cough are the common features in patients presenting with the syndrome. However, the clinical and radiographic characteristics of atypical pneumonia are not useful in differentiating these pathogens from usual bacterial pathogens such as *S. pneumoniae* and *H. influenzae*. The exclusion of common extracellular pathogens and a response to empirical therapy with macrolides or quinolones are the usual strategy of management. In our cohort, most of the common bacterial pathogens were ruled out, in addition to viral diseases such as influenza and respiratory syncytial virus infection. Moreover, lack of a response to the initial antimicrobial treatment we provided

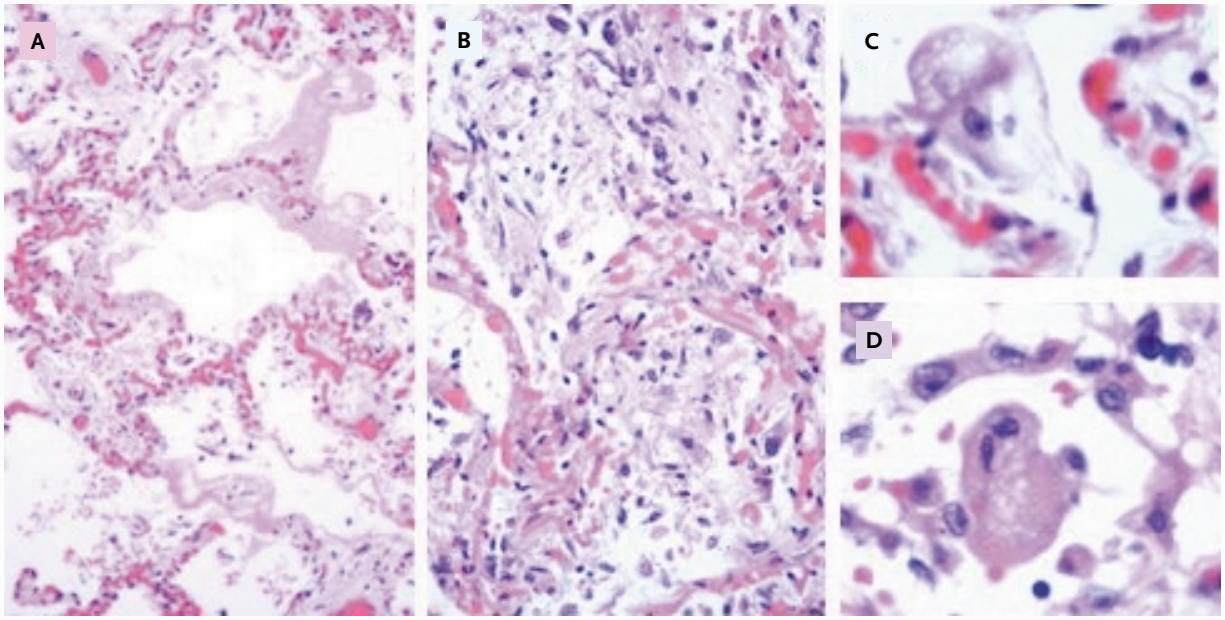


Figure 4. Lung-Biopsy Specimen Obtained at Autopsy.

Panel A shows diffuse alveolar damage with pulmonary congestion, edema, and formation of hyaline membrane (hematoxylin and eosin, ×100). Panel B shows the organizing phase of diffuse alveolar damage, with scanty interstitial inflammatory-cell infiltrates (hematoxylin and eosin, ×200). Panels C and D show vacuolated and multinucleated pneumocytes (hematoxylin and eosin, ×400).

led to the suspicion that we were dealing with a novel virus that causes lower respiratory tract infection. So far, there have been only preliminary data reported on the causative agent of SARS, and metapneumovirus and coronavirus have been implicated.[5] The relevance of histologic features such as vacuolated and multinucleated pneumocytes in the pathogenesis of SARS remains to be determined. As of this writing, no reliable diagnostic test is available. In the first 138 cases, we have identified several cardinal symptoms of SARS. Besides fever, chills, and rigor, which were present in more than 70 percent of cases, cough was present in more than 50 percent and dizziness in more than 40 percent of cases. Rigor may represent the viremic phase of the disease, which subsided gradually as the illness progressed. In addition, moderate lymphopenia and its subsequent progression, thrombocytopenia, a prolonged activated partial-thromboplastin time, elevated lactate dehydrogenase and creatine kinase levels, and elevated alanine aminotransferase levels were prevalent in the early phase of the illness in our cohort; all these findings are quite different from those associated with pneumonia caused by usual bacterial pathogens. Although these symptoms and laboratory findings are nonspecific, the constellation of these features should alert medical practitioners to the possibility of SARS.[9]

We have also found that the chest radiograph offers an important diagnostic clue to this condition. Typically, our patients presented with unilateral, predominantly peripheral areas of consolidation. After approximately one week, it progressed rapidly to bilateral patchy consolidation, and the extent of the lung opacities was correlated with the deterioration in respiratory function. In cases in which plain chest radiographs appeared normal in the presence of a high spiking fever and lymphopenia, CT of the thorax was a sensitive imaging approach for the diagnosis. The characteristic finding on CT was bilateral peripheral air-space ground-glass consolidation mimicking that in bronchiolitis obliterans organizing pneumonia. In fact, the similarity of this radiographic picture to that of bronchiolitis obliterans organizing pneumonia and the similarity of the histologic features to those of early ARDS in postmortem studies have prompted us to

use corticosteroid in combination with ribavirin for the treatment of SARS. In ARDS and particularly in bronchiolitis obliterans organizing pneumonia, corticosteroid therapy has been used with some success.[7] The majority of our cohort appeared to have a response to corticosteroid therapy, in addition to ribavirin, with resolution of fever and lung opacities within two weeks.

In this study, we were able to identify some clinical and laboratory features on presentation that were associated with the adverse clinical outcome of respiratory failure requiring care in the ICU or death. Univariate analyses showed that advanced age, male sex, a high neutrophil count, a high peak creatine kinase level, high initial and peak lactate dehydrogenase levels, and a low serum sodium level were associated with an adverse outcome. Only advanced age, a high neutrophil count, and a high peak lactate dehydrogenase level were independent predictors. Since high lactate dehydrogenase levels are often seen in association with tissue damage, we propose that this finding indicates more extensive lung injury. The significant association between a high neutrophil count and an adverse outcome remains to be explained. All five patients who died had major coexisting disorders; however, in our analyses, coexisting illness was not correlated with a poor outcome, probably because of the small number of such patients.

SARS has already become a global health hazard, and its high infectivity is alarming. The discovery of the infective agent and studies of its behavior are crucial to an understanding of this new disease. A reliable, rapid diagnostic test, based on blood samples or nasopharyngeal aspirates, is of great importance in the future management of this disease. Until such a diagnostic test is available, a clear picture of its clinical presentation will help physicians be on the alert for this condition. Early recognition, prompt isolation, and appropriate therapy are the keys in combating this deadly infection.

We wish to dedicate this report to the patients we have described, many of whom are our colleagues and their family members, together with medical students from the Faculty of Medicine, Chinese University of Hong Kong. We are also indebted to the many members of the frontline medical and nursing staff who demonstrated selfless and heroic devotion to duty in the face of this outbreak, despite the potential threat to their own lives and those of their families.

REFERENCES

1. World Health Organization. Cumulative number of reported cases (SARS) from 1 February to 27 March 2003. (Accessed April 4, 2003, at http://www.who.int/csr/sarscountry/2003_03_27.)
2. Centers for Disease Control and Prevention. Severe acute respiratory syndrome (SARS) updated interim case definition. (Accessed April 4, 2003, at http://www.cdc.gov/ncidod/sars/casedefinition.htm.)
3. Barlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000;31:347-82.
4. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730-54.
5. Update: outbreak of severe acute respiratory syndrome — worldwide, 2003. MMWR Morb Mortal Wkly Rep 2003;52:241-8.
6. Muller NL, Staples CA, Miller RR. Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. AJR Am J Roentgenol 1990;154:983-7.
7. Epler GR. Bronchiolitis obliterans organizing pneumonia. Arch Intern Med 2001;161:158-64.
8. Centers for Disease Control and Prevention. Updated interim domestic infection control guidance in the health care and community setting for patients with suspected SARS. (Accessed April 4, 2003, at http://www.cdc.gov/ncidod/sars/infectioncontrol.htm.)
9. Preliminary clinical description of severe acute respiratory syndrome. MMWR Morb Mortal Wkly Rep 2003;52:255-6.